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LUTONIX® 035 Drug Coated Balloon PTA Catheter

Meeting of the Circulatory System Devices Panel Regarding Paclitaxel-Coated Products Indicated for Peripheral Arterial Disease (PAD)

June 19-20, 2019

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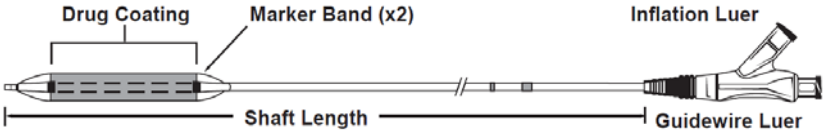
1 Introduction and Executive Summary

The LUTONIX® 035 Drug Coated Balloon Percutaneous Transluminal Angioplasty (PTA) Catheter (LUTONIX DCB) is a drug coated balloon with a paclitaxel dose density of 2 µg/mm^2. The LUTONIX DCB is available in balloon sizes from 4 – 7mm in diameter and 40 – 220mm in length for a drug dose range of 1.0mg – 9.7mg/balloon.

Figure 1: LUTONIX Drug Coated Balloon PTA Catheter



The LUTONIX DCB has been commercially available since 2012 and is currently approved in many countries including the US, Australia, Brazil, Canada, Japan, Korea, and Taiwan, and in the European Union. Over 400,000 LUTONIX DCBs have been used globally. The product has not been withdrawn from the market for safety reasons in any country.

The LUTONIX DCB is indicated in the US for PTA, after appropriate vessel preparation, of de novo, restenotic, or in-stent restenotic lesions up to 300mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-7mm. It is also approved in the US for Arteriovenous Fistula (AVF) and is the subject of an IDE study in below-the-knee (BTK) arteries.

Long-term safety of the LUTONIX DCB has been assessed through a combination of pre-clinical animal studies and available clinical data from over 3000 DCB patients. Animal study results indicate no long term toxicity, even at 4X the clinical dose, including downstream organ/tissue histopathology. Pharmacokinetic studies show that the paclitaxel levels in clearance organs are lower than levels after paclitaxel chemotherapy and are not detectable beyond 24 hours in plasma.

Data from over 3000 subjects are available for analysis to support assessment of device safety. Data from 1399 subjects, 1149 treated with the LUTONIX DCB and 250 treated with uncoated PTA, were included in the L2 Combined studies (LEVANT 2 randomized (L2RCT), LEVANT 2 Continued Access (L2CA) and LEVANT 2 Roll-In subjects (L2RI)) as well as two additional randomized, controlled clinical trials LEVANT 1 (L1) and LEVANT Japan (LJ).

The pivotal clinical study for safety of the LUTONIX DCB was the L2RCT. The L2RCT study enrolled patients with claudication and a significant lesion in the superficial femoral or popliteal artery. Patients were enrolled under the same protocol in two phases: an initial RCT to assess the safety and effectiveness of the LUTONIX DCB (n=316) as compared to PTA (n=160), and a second phase required to detect rare adverse events with an appropriate sample size, as a continued access study for DCB only patients. L2CA was included in the analysis of overall survival since it was a single-arm (DCB) continuation of the L2RCT. The majority of the investigational sites were the same; the protocol was also similar, including the same inclusion/exclusion criteria, follow-up timeframes and assessments. In total, 1029 DCB patients (including 56 roll-ins, 316 randomized and 657 continued access) were enrolled in the L2 Combined studies and followed out to 5 years. In addition, to ensure the most robust evaluation of safety for this review, the company collaborated with the clinical sites and recovered additional mortality data for subjects previously lost to follow-up (LTFU). These data are included in the analyses presented herein.

The L2RCT, L1 and LJ were prospective, multicenter, randomized, single-blinded clinical trials that included control arms with subjects treated with uncoated PTA. Long term clinical data are also available from other randomized and registry studies. Smaller studies and registries enrolled an additional 1867 DCB-treated subjects. Supportive data are also available from other indications, including AVF and BTK arteries.

To assess the potential for increased risk of mortality associated with the LUTONIX DCB, analysis was performed of the L2 Combined studies. Analysis of all available data sources concluded that while there was a numerical increase in the hazard ratio (HR) for mortality events compared to PTA, there was no significant difference as the confidence intervals in all cases overlapped 1.0. For the L2RCT study only, the HR for treatment increased slightly over time, from 1.14 (0.4-3.7) at year 1 to 1.68 (0.47-1.86) at year 5. For L2RCT+L2CA, the HR for treatment decreased to 1.56 at year 5. When all

RCTs were included (L1, L2RCT and LJ), the mortality signal was attenuated, with a HR of 0.74 (0.3-1.7) at year 1 and 1.33 (0.8-2.1) at year 2 (since L1 and LJ have follow-up to 2 years only). In addition, no statistical difference was found in an all-cause mortality analysis (p=0.077) or Kaplan-Meier (K-M) analysis (p=0.1048).

Although not statistically significant, because of the numerical increase in HR for DCB compared to PTA, further investigation was performed, which included adjudication of all mortality events in the L1 and L2 Combined studies by an independent Medical Advisory Board (MAB) blinded to treatment assignment. The MAB was composed of vascular interventionalists and an oncologist to ensure all potentially-related causes of death were considered. The MAB concluded that none of the deaths reported in study subjects were related to paclitaxel. Furthermore, the rates of cardiovascular and non-cardiovascular deaths were similar in both groups; there was no concentration in cause of death in the DCB group that differed from the PTA group. While this analysis does not invalidate the possibility of an unknown mechanism of paclitaxel-related death, the lack of clustering of any particular cause of death argues against a common mechanism. A covariate analysis did indicate potential differences in outcome between groups by arrhythmia history and use of statins; however, no other covariates were found to be significantly associated with outcomes.

It should be noted that 19.4% (31/160) of PTA patients and 18.4% (58/316) of DCB patients in the L2RCT population underwent a subsequent intervention with a DCB/DES which resulted in exposure to paclitaxel-eluting devices and associated drug dose. These patients showed higher 5-year survival rates than those receiving a single DCB or PTA intervention. In the three RCTs combined, reinterventions also appeared to be protective and the frequency of reintervention was greater in the PTA arms. Subjects in both groups (DCB and PTA) who subsequently underwent a reintervention with a paclitaxel device had a higher 5-year survival rate than those who did not have a reintervention. Similarly, patients requiring treatment of longer lesions, with consequently higher doses of paclitaxel, showed no statistically significant increase in risk (HR of lesion length in mm = 1.00; see **Table 7**). An analysis of initial dose by quartile also did not show a significant difference in risk (p = 0.2380). Thus, there was no apparent dose-dependent relationship to risk. Finally, studies of the LUTONIX DCB for other indications also showed no increase in mortality risk, including use in AVF stenosis and BTK.

In summary, while there was some numerical increase in risk in the L2 Combined studies, the HR confidence intervals overlapped 1.0 in all cases, and there was no evidence of a dose-dependent relationship with risk. In the worst case, looking at only the L2RCT, using multiple calculation methodologies (raw frequency data analysis, K-M and HR analysis), there was no significant difference in mortality rate at 5 years. In addition, there was no finding of paclitaxel-related death based on an independent review of all mortality events, or any clustering in the causes of death suggesting a common mechanism. Covariate analysis indicated potential differences in outcome between groups by arrhythmia history at baseline, as well as medications such as statins, but no other significant baseline demographic or clinical variables influenced outcomes. Reinterventions were found to be protective. Reintervention with a paclitaxel-coated device was also protective in both groups, which argues against a causal link between paclitaxel and mortality.

Based on these findings, BD Peripheral Intervention (BDPI) believes the LUTONIX DCB continues to offer an acceptable risk/benefit balance in appropriate patients requiring peripheral angioplasty. BDPI is committed to ensuring patient safety and minimizing risks. If the panel determines additional information is warranted, we support an industry-wide partnership with key stakeholders (physician societies, FDA, etc.) to further interrogate existing, large, observational datasets (e.g., CMS data, RAPID) to continue to collect additional safety data over an extended period (through 5 years).

2 Pre-Clinical Studies and Pharmacokinetics

Safety, Safety Margin and Pharmacokinetic (PK) animal studies were conducted out to 180 days with the LUTONIX DCB in accordance with FDA's Good Laboratory Practices (GLP) regulations (21 CFR Part 58). [1] Animal study results

[1] Eiseman. Plasma pharmacokinetics and tissue distribution of paclitaxel in CD2F1 mice. Cancer Chemother Pharmacol, 1994, Vol. 34, pp. 465-71; Innocenti. Plasma and tissue disposition of paclitaxel (Taxol) after intraperitoneal administration in mice. Drug Metab Dispos, 1995, Vol. 23, pp. 713-7; Fetterly. Pharmacokinetics of paclitaxel-containing liposomes in rats. *AAPS PharmSci.*, 2003, Vol. 5, pp. E32 1-11; Gustafson. P450

indicated no long term local or systemic toxicity. Even at a systemic dose of 37mg paclitaxel (approximately 10X the mean DCB dose of 3.5mg), there were no clinically significant findings in the treated arteries nor downstream tissue effects at 90 days.

In animals, the total drug exposure of DCB treatment for 6 months to clearance organs was lower than a 24-30 hour exposure to chemotherapy. Area Under the Curve over 180 days, $AUC_{180days}$ (h*µg/g) for the LUTONIX DCB in the femoral pharmacokinetic study was 9.19 for the kidney, 20.4 for the liver, and 118 for the lung as opposed to an $AUC_{0\text{-}24h/30h}$ for chemotherapy over 24h/30h of 34-340 h*µg/g for the kidney, 80-525 for the liver, and 34-354 for the lung.

Total systemic paclitaxel exposure from the LUTONIX DCB was also lower than Taxol chemotherapy. In the preclinical porcine PK study, paclitaxel levels in plasma decreased steadily over the first 24 hours post-treatment and were not detectable (below the limit of quantitation, <0.300 ng/mL) at 7 days. In the subsequent PK study in humans (sub-study of L2RCT), all subjects had detectable plasma paclitaxel immediately after the index procedure that decreased to less than 3ng/mL within one hour.[2] The mean elimination half-life value from the human plasma study was 6.88 hours. In addition, the total drug exposure across time was lower in the L2RCT study than for systemic chemotherapy ($AUC_{(0\text{-}\infty)}$ of Taxol ranges from 6300 to 15007 ng*h/mL for a dose of 135mg/m^2 at an infusion duration of 24 hours to a dose of 175mg/m^2 at an infusion duration of 3 hours, whereas the AUC_{last} for the LUTONIX DCB in the L2RCT study was 8.39 ng*h/mL).[3]

3 Analysis of Clinical Safety Information Associated with the LUTONIX DCB

3.1 Introduction

In an effort to critically examine a potential association between paclitaxel-coated femoropopliteal angioplasty and all-cause mortality, BDPI employed an independent third party to perform a pre-specified statistical analysis of data from the LUTONIX clinical program, focusing on the RCTs.

3.2 Data Sources and Methodology

Data from 1399 DCB subjects, 1149 treated with the LUTONIX DCB and 250 treated with uncoated PTA, were included in the L2 Combined studies and two additional randomized, controlled clinical trials (L1 and LJ). These studies are listed in **Table 1** below.

Table 1: BD/ LUTONIX Sponsored Randomized, Controlled Trials

Study	Dose/ µm^2	NCT	Enrollment Start Date	Study Design	Subjects (DCB:PTA)	Geography	Follow-Up
L1	2	NCT00930813	June, 2009	RCT	101 (49:52)	Europe	24 months
L2RCT with L2RI	2	NCT01412541	July, 2011	RCT	532 (316:160) randomized 56 DCB roll-in	US/EU	60 months
L2CA	2	NCT01628159	February, 2013	Single arm	657	US, Europe	60 months
LJ	2	NCT01816412	March, 2013	RCT	109 (71:38)	Japan	24 months
Total					**1399 (1149:250)**	**US, Europe, Japan**	**24-60 months**

induction alters paclitaxel pharmacokinetics and tissue distribution with multiple dosing. *Cancer Chemother Pharmacol*, 2005, Vol. 56, pp. 248-54; Yeh. Formulating paclitaxel in nanoparticles alters its disposition. *Pharm Res*, 2005, Vol. 22, pp. 867-74.

[2] BAW1387400r3 IFU, LUTONIX 035 Drug Coated Balloon PTA Catheter

[3] TAXOL Package Insert

In addition, while not the focus of this analysis, data are available from several other studies and registries, for a total of over 3000 DCB subjects studied:

- In-stent Restenosis Study (ISR) (NCT02063672) (53 DCB, 29 PTA), 36-month follow-up
- Long Lesion Study (NCT02013271) (118 DCB), 36-month follow-up
- Global SFA Real-World Registry (NCT01864278) (691 DCB), 24-month follow-up
- SAFE DCB Registry (NCT02424383) (1005 DCB), 36-month follow-up

To ensure maximum data were available for analysis, the company also collaborated with clinical sites and recovered data for subjects in the L2 Combined studies that had been previously lost to follow-up. These data are included in the analyses presented herein.

Deaths in these studies were originally adjudicated by a blinded, independent CEC. For the current analysis, the primary causes of death in the L1 and L2 Combined studies were re-adjudicated by an independent MAB. In order to ensure that the re-adjudication considered all causes of death which potentially may be related to paclitaxel, the MAB was comprised of both interventionalists (vascular surgeons and interventional radiologists) and oncologists experienced in the use of systemic paclitaxel chemotherapy. The MAB used a 2 +1 adjudication model whereby two adjudicators (an interventionalist and an oncologist) separately adjudicated each element of the event. If there was discordance between the first two adjudicators, a third adjudicator, always an oncologist, broke the tie.

Deaths were classified by their relationship to the device, the procedure, and paclitaxel. Using the guidelines established in Hicks et al.[4] deaths were classified[5] as cardiovascular (CV) or non-cardiovascular (NCV). The relationship of the death to paclitaxel exposure was examined with respect to the development and timing of all adverse drug reactions known to occur from the drug.[6] The MAB adjudicator was provided with narratives and source documents blinded to treatment (DCB vs. PTA). The decision tree for relatedness to paclitaxel included a table that listed nine important adverse events specified in the paclitaxel package insert (anaphylaxis (e.g., dyspnea, hypotension, urticaria), arrhythmia, hepatic dysfunction, hypertension, anemia, neutropenia/leukopenia, thrombocytopenia, neoplasm (new or recurrent), and peripheral neuropathy), along with a tenth “other” category if the adjudicator believed that another type of paclitaxel-related mechanism was causative. The adjudicator then classified paclitaxel-relatedness into one of five categories: definitely related, probably related, possibly related, unlikely related, or not related. For the purposes of the adjudication, paclitaxel-relatedness was defined as at least possibly related.

Next, the mortality rates in the DCB and PTA arms of the L2RCT and in the combined L1, L2RCT, and LJ RCTs were assessed.[7] Cox proportional hazard modeling of associations between candidate baseline covariates and death was performed.[8] Since data from the three studies are not strictly poolable, propensity analyses were performed. Where Kaplan-Meier data are displayed by year, the time points are as follows: 1 year- 365 days, 2 years- 730 days, 3 years- 1095 days, 4 years- 1460 days, and 5 years- 1825 days.

3.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics were examined in the three RCTs (L1, L2RCT, and LJ). Among the 686 subjects, there were a total of 436 DCB and 250 PTA-treated subjects. There were very few differences in the demographics and other baseline characteristics between the groups, with 62.4% and 65.2% men in the DCB and PTA cohorts, respectively. Comorbidities were characteristic of most studies of peripheral arterial interventions, with hypertension, dyslipidemia, and myocardial infarction common in both groups. Approximately one-third of subjects in

[4] Hicks KA, Mahaffey KW, Mehran R, Nissen SE. 2017 cardiovascular and stroke endpoint definitions for clinical trials. Circulation 2018;137:961-72.
[5] From the Standardized Data Collection for Cardiovascular Trials Initiative and the U.S. Food and Drug Administration.
[6] As listed in the paclitaxel package insert
[7] The L2 dataset is much larger than the datasets from the two other LEVANT RCTs. The aggregated dataset is understandably similar to the findings from L2 as evaluated alone.
[8] A group of experts blinded to outcome chose candidate variables from the group of baseline demographic and baseline characteristics common to the RCTs, eliminating variables without a plausible association with morbidity or mortality.

both groups were current smokers. Combined data showed that there were 89.2% De Novo and 10.8% recurrent lesions in the DCB group. The PTA group had 91.6% De Novo and 8.4% recurrent lesions. Calcification was reported in 56.8% of DCB and 58.6% of PTA subjects. The mean Ankle Brachial Index was similar between the two groups. Average total lesion length was 65.9mm and 66.2mm for the DCB and PTA groups, respectively. Reference vessel diameters were 4.8mm (DCB) vs. 4.9mm (PTA). The mean paclitaxel dosage across the RCTs was 3.4mg.[9]

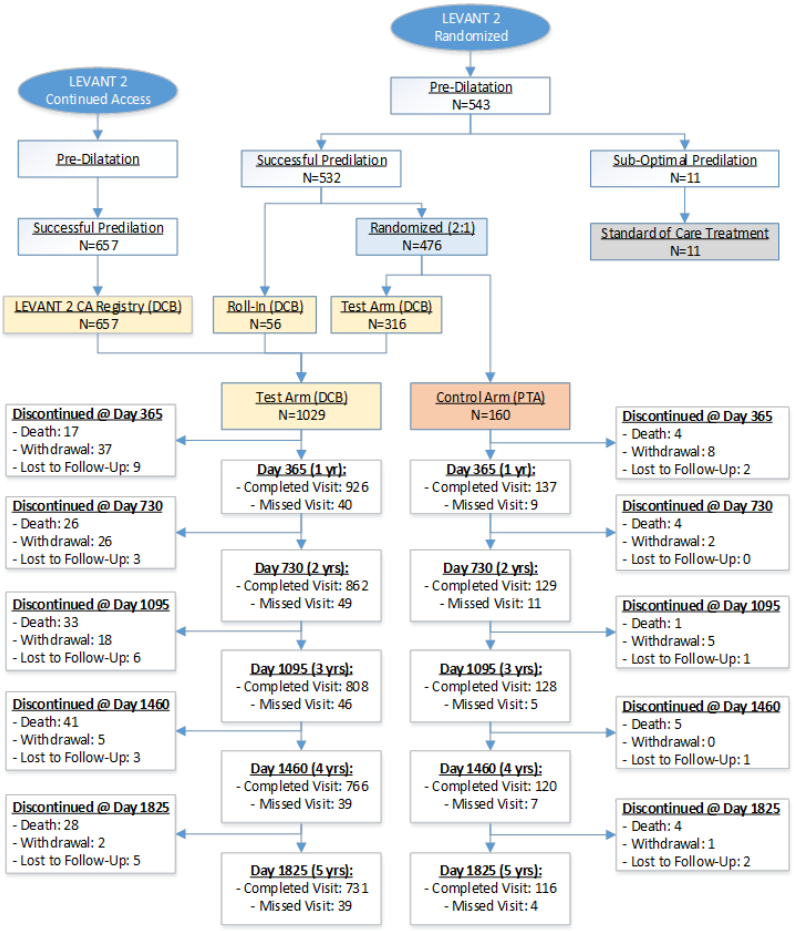
In the 3 RCTs, the percentage of DCB subjects with baseline arrhythmia was 10.8% vs. 14.0% for PTA. The percentage on statins at baseline was almost identical (72.9% for DCB vs. 72.8% for PTA).

3.4 L2 Combined Study Data

3.4.1 Subject Accountability

A consort diagram for the L2 Combined studies is provided in **Figure 2** below. The L2 Combined studies had a similar rate of discontinued subjects and a high rate of subjects evaluable for mortality at 5 years in both arms.

Figure 2: Consort Diagram – L2 Combined Studies



[9] The dose was calculated from the nominal amount of paclitaxel on each balloon size and the number and size of balloons used in each patient.

3.4.2 All-Cause Mortality Rate

A raw frequency data analysis of L2 Combined studies, including additional subjects who had previously been LTFU, showed an all-cause mortality rate of 15.99% in the DCB arm and 12.68% in the PTA arm at 5 years; this difference was not statistically significant (p=0.383), as shown in Table 2.

Table 2: All-Cause Mortality Rates in L2 Combined Studies

Time Point	L2RCT			L2 Combined	
	DCB Subjects	PTA Subjects	P-value*	All DCB	P-value*
1 Yr	1.99% (6/301)	2.67% (4/150)	0.737	1.62% (16/988)	0.322
2 Yrs	6.51% (19/292)	5.41% (8/148)	0.834	4.50% (43/955)	0.673
3 Yrs	9.86% (28/284)	6.29% (9/143)	0.275	8.18% (76/929)	0.509
4 Yrs	16.07% (45/280)	9.79% (14/143)	0.102	12.81% (118/921)	0.343
5 Yrs	19.93% (55/276)	12.68% (18/142)	0.077	15.99% (146/913)	0.383

* *Fisher's Exact Test*

3.4.3 All-Cause Mortality: Repeat Procedures as a Time-Dependent Covariate

The all-cause mortality over time is summarized for the L2RCT study in **Table 3**. Three analyses were performed: index procedure (treatment with DCB vs. PTA), with adjustment for reinterventions (whether with a DCB/DES or not) and with adjustment for reinterventions only with a DCB/DES. The HR for treatment with DCB increased slightly over time, from 1.14 at year 1 to 1.68 at year 5. The confidence intervals overlapped 1.0 at all timepoints. When treatment was adjusted for any additional post-procedure reintervention (defined as PTA/DCB/DES, stent, laser, atherectomy or other in the treated limb) as a time-dependent covariate, the HR increased from 0.98 to 1.58 between 1 and 5 years, and when treatment was adjusted for DCB/DES only reintervention, the HR increased from 1.0 to 1.63 between 1 and 5 years.

Table 3: L2RCT All-Cause Mortality Hazard Ratio Over Time

Covariate	Year 1	Year 2	Year 3	Year 4	Year 5
Treatment with DCB	1.14 (0.4-3.7)	1.40 (0.6-3.7)	1.70 (0.65-1.43)	1.69 (0.5-1.7)	1.68 (0.47-1.86)
Treatment adjusted for Post-index Procedure	0.98 (0.3-3.3)	1.58 (0.9 – 2.9)	1.68 (0.8 – 3.5)	1.58 (0.9 – 2.9)	1.58 (0.91-2.7)
Treatment adjusted for DCB/DES Post-index rocedure	1.0 (0.30-3.3)	1.63 (0.9 – 3.0)	1.62 (0.8 – 3.4)	1.63 (0.9 – 2.9)	1.63 (0.9-2.8)

The HR was also calculated using reinterventions with paclitaxel as the time dependent covariate, with follow-up through 5 years. There was a small decrease in the HR of death including either any reintervention or reinterventions with paclitaxel as time-dependent covariates, as shown in **Table 4** below.

Table 4: L2RCT All-Cause Mortality Cox PH Model

Covariate	Hazard Ratio (95% CI)	P-value for Model	AIC	P-value for Schoenfeld test for PH
Treatment with DCB	1.68 (0.47-1.86)	0.079	853	0.6
Treatment adjusted for Post-index Procedure	1.58 (0.91-2.7)	0.10	825	0.4
Treatment adjusted for DCB/DES Post-index Procedure	1.63 (0.9-2.8)	0.08	836	0.5

To look at the full L2 Combined dataset, a propensity analysis of L2CA and L2RI patients with the L2RCT PTA cohort was performed. Having propensity matched the two populations using the stratification method, the adjusted Hazard Ratio at 5 years was 1.59 (95% CI 0.85-2.99, p = 0.1502). Next, the propensity analysis was repeated, including L2RCT DCB

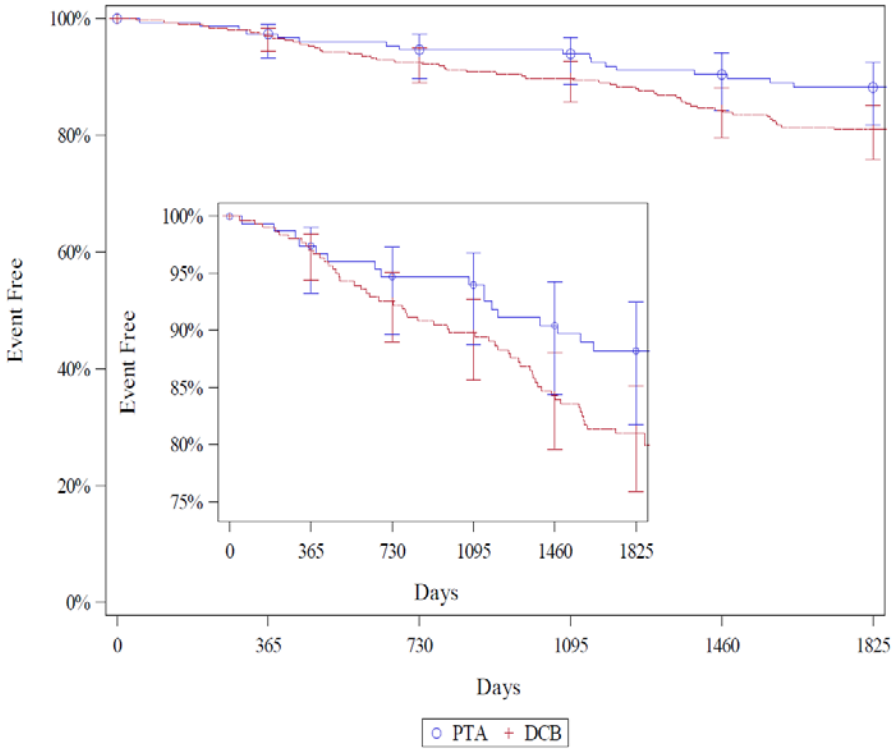
cohort with L2CA/L2RI patients. After propensity matching the populations, the adjusted Hazard Ratio at 5 years was 1.56 (95% CI 0.88-2.77, p = 0.125).

3.5 Overall Survival

Patient survival through 5 years was evaluated for each of the three RCTs, as described below. Survival was also calculated for the L2 Combined studies, including some patients that were formerly LTFU.

Survival for the L2RCT is shown in **Figure 3**. Overall, the 5-year rate of survival for DCB patients (N=316) was 81.1 ± 2.3%, at 5 years compared to the PTA patients (N=160), 87.6 ± 2.7%, but this difference was not statistically significant (p = 0.1048).

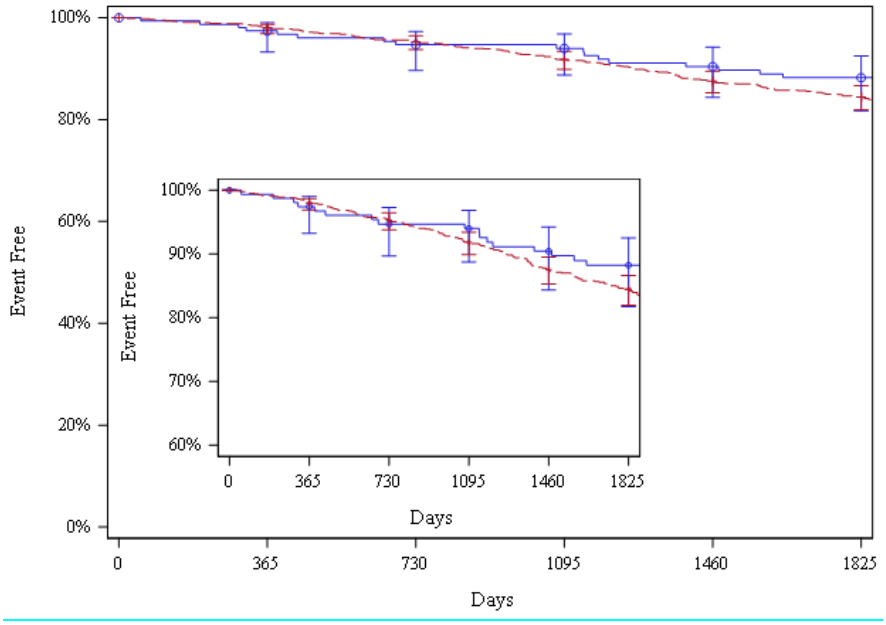
Figure 3: Survival in the L2RCT (P = 0.1048)



LEVANT 2 DCB Patients						
Interval	**Baseline**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
# Entered	316	316	288	268	253	233
# Censored	0	18	7	7	5	98
# Events	0	9	13	8	15	9
Survival	100.0%	97.1%	92.6%	89.8%	84.4%	81.1%
Greenwood SE [%]	0.0%	1.0%	1.5%	1.8%	2.1%	2.3%
95% Confidence Interval		94.42%-98.46%	88.99%-95.07%	85.73%-92.76%	79.66%-88.12%	76.06%-85.21%
LEVANT 2 PTA Patients						
Interval	**Baseline**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
# Entered	160	160	146	140	133	127
# Censored	0	10	2	6	0	55
# Events	0	4	4	1	6	3
Survival	100.0%	97.4%	94.7%	94.0%	89.8%	87.6%
Greenwood SE [%]	0.0%	1.3%	1.8%	1.9%	2.5%	2.7%
95% Confidence Interval		93.26%-99.02%	89.71%-97.32%	88.80%-96.84%	83.59%-93.71%	81.03%-92.01%

A similar analysis was repeated for the L2 Combined studies. Survival through 5 years was 84.4% + 1.2% vs. 88.2% ± 2.7% in the DCB and PTA groups, respectively (p = 0.2208).

Figure 4: Survival in L2 Combined Studies (P = 0.2208)



LEVANT 2 All DCB Patients (CA, Roll-in, and RCT)

Interval	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
# Entered	1024	1024	955	899	843	795
# Censored	0	47	30	24	9	394
# Events	0	20	26	32	39	27
Survival	100.0%	98.0%	95.3%	91.8%	87.6%	84.4%
Greenwood SE [%]	0.0%	0.4%	0.7%	0.9%	1.1%	1.2%
95% Confidence Interval		96.91%-98.70%	93.76%-96.45%	89.90%-93.40%	85.27%-89.51%	81.93%-86.64%

LEVANT 2 PTA Patients

Interval	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
# Entered	160	160	146	139	132	127
# Censored	0	10	3	6	0	56
# Events	0	4	4	1	5	3
Survival	100.0%	97.4%	94.7%	94.0%	90.4%	88.2%
Greenwood SE [%]	0.0%	1.3%	1.8%	1.9%	2.4%	2.7%
95% Confidence Interval		93.26%-99.02%	89.67%-97.31%	88.75%-96.83%	84.36%-94.22%	81.73%-92.52%

For the L1 study, the 2-year survival of patients in the DCB (N=45) and PTA (N=43) treatment arms was similar; 91.6% ± 4.0% and 92.0% ± 3.8%, respectively (p = 0.8334). For the LJ study, at 2 years, survival was 97.2% ± 2.0% in the 70 DCB patients, compared with 91.4% ± 4.7% in the 35 PTA patients (p = 0.1888).

3.6 Independent Adjudication of Mortality Events

MAB-adjudicated deaths for L1 and L2 Combined are summarized in **Figure 5** and **Table 5**. The rates of cardiovascular (CV) and non-cardiovascular (NCV) deaths were similar in both groups. Both groups also had similar rates of neoplastic and non-neoplastic related deaths. The MAB was able to classify the cause of death in all but 19 patients; 2/22 PTA deaths (9.1%) and 17/151 DCB deaths (11.3%).

Using the classifications of Hicks et al.,[10] the most common cause of cardiovascular death was heart failure, responsible for 37.5% of deaths in the PTA group and 38.2% in the DCB group. The rate of sudden cardiac deaths is the same between groups (12.5% for PTA and 12.7% for DCB). The most common cause of NCV death and the most frequent

[10] Hicks KA, Mahaffey KW, Mehran R, Nissen SE. 2017 cardiovascular and stroke endpoint definitions for clinical trials. Circulation 2018;137:961-72.

cause of death overall was neoplasm, accounting for 50.0% of deaths in both the PTA and DCB groups. There was no clustering in any category of cause of death; the proportion of deaths in the PTA and DCB arms was similar for every category. While this analysis does not invalidate the possibility of an unknown mechanism of paclitaxel-related death, the lack of clustering of any particular cause of death argues against a common mechanism.

None of the deaths were adjudicated as definitely, probably, or possibly related to paclitaxel. Among the 173 deaths, only one was classified as paclitaxel-related by any adjudicator. This death occurred from infection 12 months after the index procedure and was classified by one MAB member, an interventionalist, as "possibly related" to paclitaxel. The death was classified as "not related" and "unrelated" by the other two adjudicators, both of whom were oncologists. The final 2 + 1 adjudication result for paclitaxel relatedness of this death was "not related."

Figure 5: Distribution of Causes of Death in L1 and L2 Combined

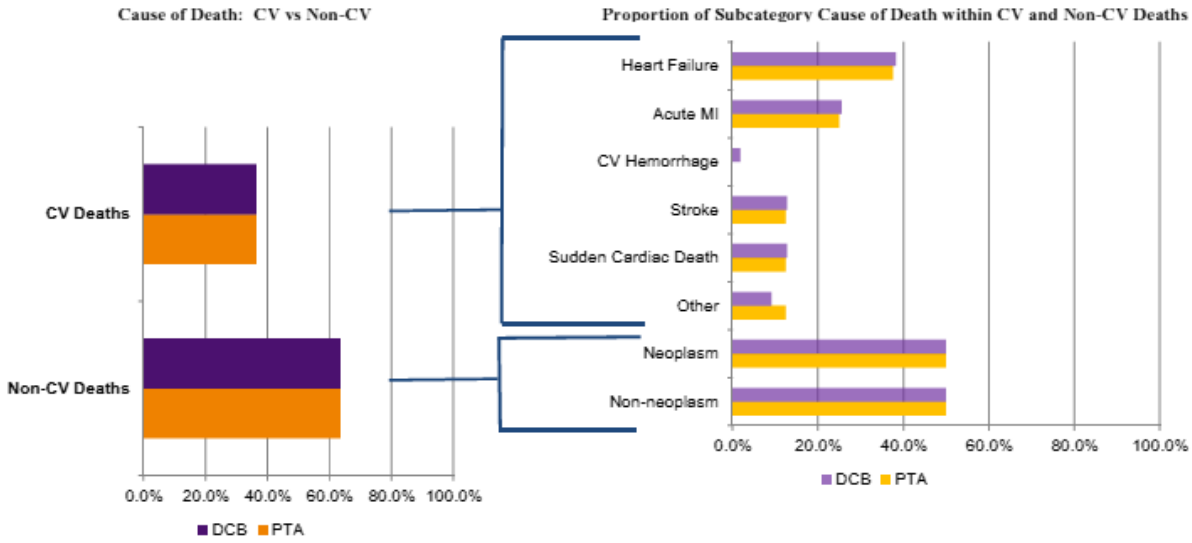


Table 5: Summary of Adjudicated Deaths

Cause of death	L1 (n=9)		L2RCT+L2RI (n= 81)		L2CA (n=83)	All (n=173)		
	PTA (n=5)	DCB (n=4)	PTA (n=17)	DCB (n=64)	DCB (n=83)	PTA (n=22)	DCB (n=151)	P Value*
Cardiovascular deaths	**60.0% (3/5)**	**50.0% (2/4)**	**29.4% (5/17)**	**35.9% (23/64)**	**36.1% (30/83)**	**36.4% (8/22)**	**36.4% (55/151)**	>.999
Heart failure	66.7% (2/3)	0.0%	20.0% (1/5)	21.7% (5/23)	53.3% (16/30)	37.5% (3/8)	38.2% (21/55)	>.999
Acute MI	33.3% (1/3)	50.0% (1/2)	20.0% (1/5)	30.4% (7/23)	20.0% (6/30)	25.0% (2/8)	25.5% (14/55)	>.999
CV hemorrhage	0.0%	0.0%	0.0%	0.0%	3.3% (1/30)	0.0%	1.8% (1/55)	NE
Stroke	0.0%	0.0%	20.0% (1/5)	21.7% (5/23)	6.7% (2/30)	12.5% (1/8)	12.7% (7/55)	>.999
Sudden cardiac death	0.0%	0.0%	20.0% (1/5)	21.7% (5/23)	6.7% (2/30)	12.5% (1/8)	12.7% (7/55)	>.999
Other	0.0%	50.0% (1/2)	20.0% (1/5)	4.3% (1/23)	10.0% 3/30	12.5% (1/8)	9.1% (5/55)	0.573
Non-CV deaths	**40.0% (2/5)**	**50.0% (2/4)**	**70.6% (12/17)**	**64.1% (41/64)**	**63.9% (53/83)**	**63.6% (14/22)**	**63.6% (96/151)**	>.999
Neoplasm	50.0% (1/2)	50.0% (1/2)	50.0% (6/12)	56.1% (23/41)	45.3% (24/53)	50.0% (7/14)	50.0% (48/96)	>.999
Bladder	0.0%	0.0%	0.0%	0.0%	4.2% (1/24)	0.0%	2.1% (1/48)	NE

Cause of death	L1 (n=9)		L2RCT+L2RI (n= 81)		L2CA (n=83)	All (n=173)		
	PTA (n=5)	DCB (n=4)	PTA (n=17)	DCB (n=64)	DCB (n=83)	PTA (n=22)	DCB (n=151)	P Value*
Blood-based	0.0%	0.0%	0.0%	4.3% (1/23)	0.0%	0.0%	2.1% (1/48)	NE
Brain	0.0%	0.0%	0.0%	8.7% (2/23)	0.0%	0.0%	4.2% (2/48)	NE
Breast	0.0%	0.0%	0.0%	0.0%	4.2% (1/24)	0.0%	2.1% (1/48)	NE
Gastrointestinal	100.0% (1/1)	0.0%	50.0% (3/6)	13.0% (3/23)	20.8% (5/24)	28.6% (4/14)	16.7% (8/48)	0.457
Lung	0.0%	100.0% (1/1)	50.0% (3/6)	39.1% (9/23)	25.0% (6/24)	21.4% (3/14)	33.3% (16/48)	0.519
Pancreatic	0.0%	0.0%	0.0%	4.3% (1/23)	0.0%	0.0%	2.1% (1/48)	NE
Prostate	0.0%	0.0%	0.0%	4.3% (1/23)	0.0%	0.0%	2.1% (1/48)	NE
Uterine/Cervical	0.0%	0.0%	0.0%	0.0%	4.2% (1/24)	0.0%	2.1% (1/48)	NE
Other	0.0%	0.0%	0.0%	26.1% (6/23)	29.2% (7/24)	0.0%	27.1% (13/48)	NE
Undetermined	0.0%	0.0%	0.0%	0.0%	12.5% (3/24)	0.0%	6.3% (3/48)	NE
Non-neoplasm	50.0% (1/2)	50.0% (1/2)	50.0% (6/12)	43.9% (18/41)	54.7% (29/53)	50.0% (7/14)	50.0% (48/96)	>.999
Hepatobiliary	0.0%	0.0%	0.0%	0.0%	3.4% (1/29)	0.0%	2.1% (1/48)	NE
Infection	0.0%	100.0% (1/1)	50.0% (3/6)	38.9% (7/18)	24.1% (7/29)	42.9% (3/7)	31.3% (15/48)	0.671
Inflammatory†	0.0%	0.0%	0.0%	0.0%	3.4% (1/29)	0.0%	2.1% (1/48)	NE
Pulmonary	0.0%	0.0%	16.7% (1/6)	11.1% (2/18)	20.7% (6/29)	14.3% (1/7)	16.7% (8/48)	0.341
Renal	0.0%	0.0%	0.0%	5.6% (1/18)	3.4% (1/29)	14.3% (1/7)	4.2% (2/48)	>.999
Suicide	0.0%	0.0%	0.0%	5.6% (1/18)	3.4% (1/29)	0.0%	4.2% (2/48)	NE
Trauma	0.0%	0.0%	0.0%	5.6% (1/18)	3.4% (1/29)	0.0%	4.2% (2/48)	NE
Undetermined	100.0% (1/1)	0.0%	33.3% (2/6)	33.3% (6/18)	37.9% (11/29)	28.6% (2/7)	35.4% (17/48)	>.999

NE- Not evaluable
**Fisher's exact test*
† e.g. SIRS, immune, autoimmune, may include anaphylaxis from environmental factors.

In sum, there was no causal link identified between paclitaxel and any of the deaths, and the types of deaths were similar in both groups, showing no clustering around cause of death in the DCB group.

3.7 Analysis of Potential Dose-Dependent Mortality Risk

Two types of analyses were performed to assess the potential relationship between dosage or exposure and mortality risk: analysis of patients with additional exposures due to reintervention compared to those with only a single exposure, and evaluation of those with long lesions (receiving higher dose) compared to those who did not have long lesions. Each analysis is presented below.

3.7.1 Analysis by Reintervention

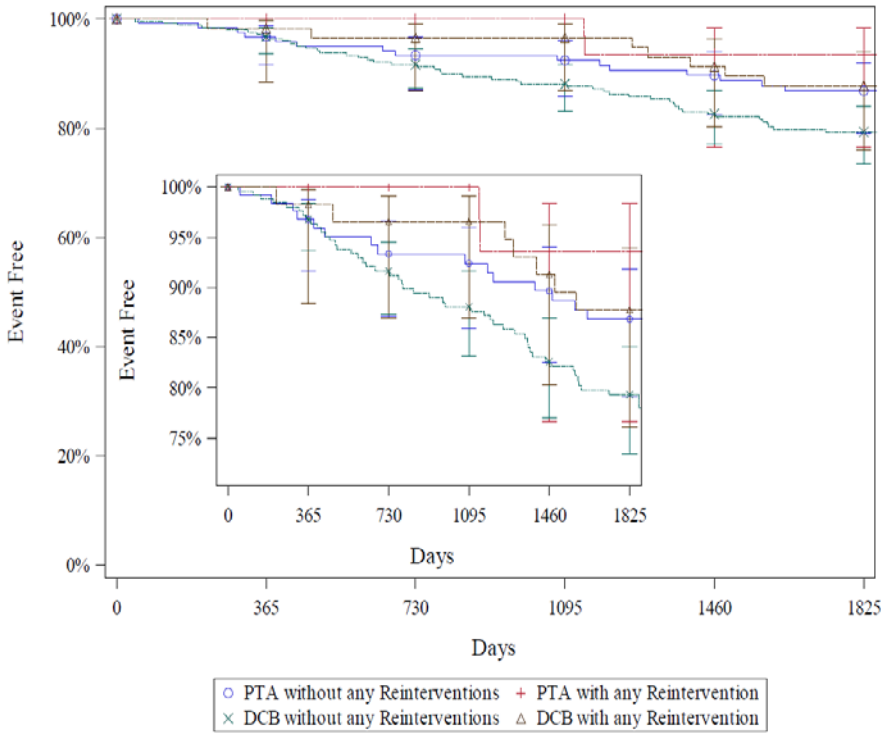
L2RCT DCB subjects without a reintervention had a lower estimated survival rate at 5 years (79.3 ± 2.7%) than DCB subjects who received a reintervention at the same timepoint (87.8 ± 4.3%). The PTA group showed a similar decrease in Kaplan-Meier survival in the subjects that did not receive reintervention compared to those that did (86.8 ± 3.2% vs. 93.5 ± 4.4%). In both groups, subjects that received a reintervention had a higher rate of survival than those that did not. See **Figure 6**.

The timepoint when first reintervention occurred in L2RCT is shown in **Table 6**.

Table 6: L2RCT Timepoint of First Reintervention

	DCB	PTA
Year 1	10	7
Year 2	10	7
Year 3	12	4
Year 4	15	11
Year 5	11	2
Total Patients with Reinterventions	58	31

Figure 6: Freedom from All-Cause Mortality (Any Reintervention) - L2RCT



DCB Subjects with Any Reintervention

Interval	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
# Entered	58	58	57	56	56	52
# Censored	0	0	0	0	1	20
# Events-Deaths	0	1	1	0	3	2
Survival	100.0%	98.3%	96.6%	96.6%	91.3%	87.8%
Greenwood SE [%]	0.0%	1.7%	2.4%	2.4%	3.7%	4.3%
95% Confidence Interval		88.38%-99.76%	86.91%-99.13%	86.91%-99.13%	80.32%-96.28%	76.05%-93.98%

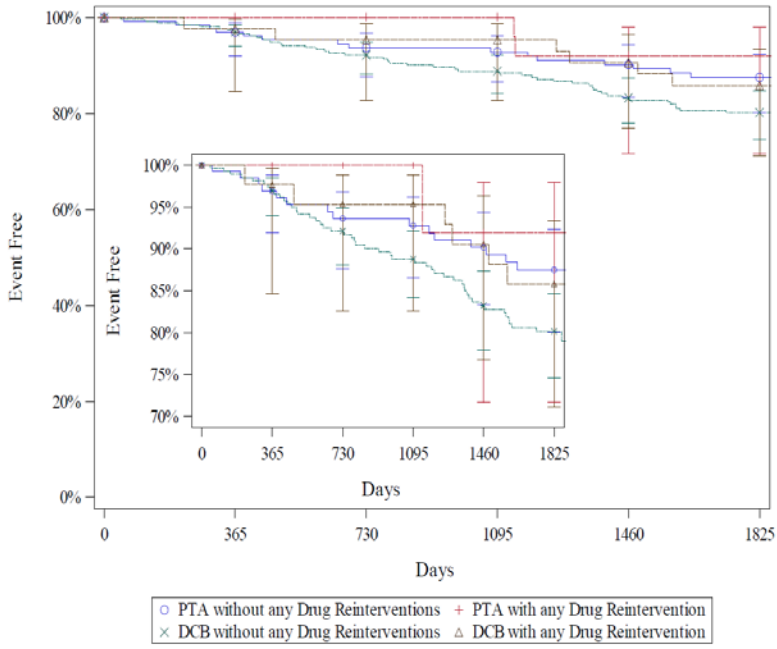
DCB Subjects without Any Reintervention

Interval	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
# Entered	258	258	231	211	196	178
# Censored	0	18	8	7	6	78
# Events-Deaths	0	8	12	8	12	7
Survival	100.0%	96.8%	91.6%	88.1%	82.6%	79.3%
Greenwood SE [%]	0.0%	1.1%	1.8%	2.1%	2.5%	2.7%
95% Confidence Interval		93.65%-98.37%	87.32%-94.52%	83.19%-91.62%	77.01%-86.93%	73.41%-84.04%

PTA Subjects with Any Reintervention						
Interval	**Baseline**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
# Entered	31	31	31	31	31	29
# Censored	0	0	0	0	0	12
# Events-Deaths	0	0	0	0	2	0
Survival	100.0%	100.0%	100.0%	100.0%	93.5%	93.5%
Greenwood SE [%]	0.0%	0.0%	0.0%	0.0%	4.4%	4.4%
95% Confidence Interval					76.59%-98.35%	76.59%-98.35%
PTA Subjects without Any Reintervention						
Interval	**Baseline**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
# Entered	129	129	115	108	101	98
# Censored	0	10	3	6	0	44
# Events-Deaths	0	4	4	1	3	3
Survival	100.0%	96.8%	93.3%	92.4%	89.7%	86.8%
Greenwood SE [%]	0.0%	1.6%	2.3%	2.4%	2.8%	3.2%
95% Confidence Interval		91.61%-98.77%	87.09%-96.61%	85.91%-95.98%	82.49%-94.00%	79.09%-91.87%

The 5-year survival rate for L2RCT DCB subjects that underwent reinterventions with paclitaxel devices was also higher than those that did not have a reintervention with paclitaxel devices, 85.8 ± 5.4% vs. 80.2 ± 2.6%, respectively. This trend was also observed in the PTA treatment arm; patients initially treated with PTA who subsequently underwent a reintervention with a paclitaxel device had higher 5-year survival rates than those that did not have a reintervention with paclitaxel devices, 92.0% ± 5.4% vs. 87.5% ± 3.0%, respectively. See **Figure 7**.

Figure 7: Freedom from All-Cause Mortality (Paclitaxel Device Reintervention) - L2RCT



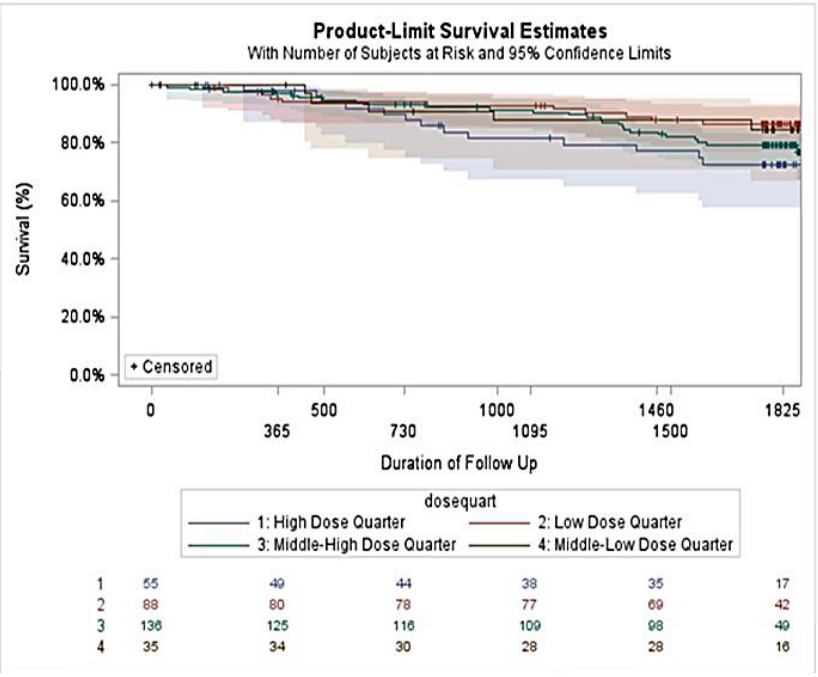
DCB Subjects with Any Paclitaxel Device Reintervention						
Interval	**Baseline**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
# Entered	43	43	42	41	41	38
# Censored	0	0	0	0	1	15
# Events-Deaths	0	1	1	0	2	2
Survival	100.0%	97.7%	95.3%	95.3%	90.6%	85.8%
Greenwood SE [%]	0.0%	2.3%	3.2%	3.2%	4.5%	5.4%
95% Confidence Interval		84.62%-99.67%	82.66%-98.82%	82.66%-98.82%	76.81%-96.36%	71.11%-93.37%

DCB Subjects Without Any Paclitaxel Device Reintervention						
Interval	**Baseline**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
# Entered	273	273	246	226	211	192
# Censored	0	18	8	7	6	83
# Events-Deaths	0	8	12	8	13	7
Survival	100.0%	97.0%	92.1%	88.8%	83.2%	80.2%
Greenwood SE [%]	0.0%	1.1%	1.7%	2.0%	2.4%	2.6%
95% Confidence Interval		94.00%-98.47%	88.06%-94.85%	84.18%-92.13%	77.91%-87.38%	74.55%-84.68%
PTA Subjects with Any Paclitaxel Device Reintervention						
Interval	**Baseline**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
# Entered	25	25	25	25	25	23
# Censored	0	0	0	0	0	11
# Events-Deaths	0	0	0	0	2	0
Survival	100.0%	100.0%	100.0%	100.0%	92.0%	92.0%
Greenwood SE [%]	0.0%	0.0%	0.0%	0.0%	5.4%	5.4%
95% Confidence Interval					71.64%-97.94%	71.64%-97.94%
PTA Subjects Without Paclitaxel Device Reintervention						
Interval	**Baseline**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
# Entered	135	135	121	114	107	104
# Censored	0	10	3	6	0	45
# Events-Deaths	0	4	4	1	3	3
Survival	100.0%	96.9%	93.6%	92.8%	90.2%	87.5%
Greenwood SE [%]	0.0%	1.5%	2.2%	2.3%	2.7%	3.0%
95% Confidence Interval		91.99%-98.83%	87.68%-96.77%	86.56%-96.18%	83.33%-94.31%	80.10%-92.28%

3.7.2 Analysis by Dose

In the L2RCT, the effect of paclitaxel dose at the index procedure on survival was analyzed by quartile (see **Figure 8**). The differences were not statistically significant (p = 0.2380).

Figure 8: Survival in the L2RCT by Dose Quartile (P = 0.2380)



Test of Equality over Strata			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	4.2269	3	0.2380

the 25.0000 percentile, mgdose	the 50.0000 percentile, mgdose	the 75.0000 percentile, mgdose	the 100.0 percentile, mgdose
1.88496	3.14159	5.02655	11.3097

3.8 Analysis by Baseline Variables

An analysis was performed for predictors of mortality, using all available variables except treatment. **Table 7** summarizes the top variables that were associated with mortality in the L2RCT study. Arrhythmia at baseline was the most significant predictor of mortality (risk factor; HR 2.84, P < 0.0001), followed by statin use at baseline (protective; HR 0.47, p = 0.003). Other less significant variables in the model included ACE inhibitors (risk factor) and lesion length (risk factor).

Table 7: Top Variables That Predict Mortality - L2RCT

Variables	Hazard Ratio	Lower CL	Upper CL	P-value
Arrhythmia at Baseline (yes/no)	2.84	1.58	5.08	<0.0001
Statins (yes/no)	0.47	0.29	0.77	0.003
ACE Inhibitors (yes/no)	1.57	0.98	2.52	0.06
Lesion Length (per mm)	1.00	1.00	1.01	0.09
CL- Confidence limit				

Additional analyses of these covariates are being undertaken.

3.9 L2RCT and Other Randomized Studies

In addition to the L2RCT study, two additional prospective, multicenter, randomized controlled trials have been conducted comparing LUTONIX DCB to standard PTA for treatment of the femoropopliteal artery.

The L1 study enrolled subjects in Europe and included treatment of femoropopliteal arteries with and without stenting (post-dilatation with DCB/PTA) under a similar protocol to L2; follow-up was through 2 years. The LJ study followed the same protocol as the L2 study for treatment of the femoropopliteal artery but with enrollment of subjects in Japan and follow-up through 2 years.

In total, these two RCTs introduce an additional 210 randomized subjects (120 DCB and 90 PTA).

Details of the mortality analysis with inclusion of the additional randomized patients are below (**Table 8**). As can be seen, when the additional randomized control studies were included, the mortality signal was attenuated, with the limitation that these data are available to 2 years only. The HR for treatment with DCB increased from 0.74 to 1.33 from year 1 to 2. The HR for treatment and any post-index procedure reintervention also increased between the years, but at a lower magnitude. When the time dependent variable of reintervention (post-index procedures) was considered in the analysis, the HR decreased to less than 1.0.[11] These observations suggest that post-index procedure reinterventions play an important role in mortality over follow-up; reinterventions appear to be protective. While speculative, more early reinterventions may imply a greater attention to behavioral factors such as smoking cessation and exercise programs in addition to medication changes – particularly statin therapy and other agents known to attenuate atherosclerotic progression.

Table 8: L1, L2RCT and LJ All-Cause Mortality Hazard Ratio Over Time

Covariate	Year 1	Year 2
Treatment with DCB	0.74 (0.3 – 1.7)	1.33 (0.8 – 2.1)
Treatment adjusted for Post-index Procedure	0.60 (0.3 – 1.4)	0.90 (0.5 – 1.6)

[11] In all cases, the confidence intervals for the HRs overlapped 1.0; the relationships did not attain significance.

3.10 Summary of Safety Data from Additional LUTONIX Studies and Registries

Rates of all-cause mortality in additional LUTONIX DCB studies and registries are shown in **Table 9** below.

Table 9: All-Cause Mortality by Study

Study	Time Point	DCB	PTA	Fisher's Exact P-value
ISR	36 Months	12.0% (6/50)	13.0% (3/23)	1.000
Long Lesion	36 Months	8.3% (9/108)	NA	NA
Global Registry	24 Months	5.1% (34/667)	NA	NA

In addition, the company is currently conducting the SAFE-DCB registry (1005 patients, 36-month follow-up, US), which is not included in the table above because it is ongoing and it is conducted as an open label registry study with site/investigator reporting only (no independent CEC, no independent adjudication of deaths, and limited monitoring).

3.11 Other Indications (BTK and AVF)

The LUTONIX DCB has been studied in multiple vessel beds in similar total doses ranging from 2.8-3.5mg. The ongoing BTK IDE study is a prospective, global, multicenter, single-blind, randomized, controlled study comparing the LUTONIX DCB vs. PTA for treatment of BTK arteries. A total of 442 randomized (2:1) subjects (287 DCB and 155 PTA) were enrolled. Study follow-up is 36 months. With 52% of the subjects evaluated to 36 months, the overall death rate for DCB and PTA are 25.9% (41/158) and 29.2% (21/72) respectively, p=0.542.

The AV IDE study was a prospective, global, multicenter, randomized, controlled study comparing the LUTONIX DCB vs. PTA for the treatment of dysfunctional AV fistulae. A total of 285 randomized subjects (141 DCB and 144 PTA) were enrolled. Study follow-up was 24 months. The overall death rate at 24 months for DCB and PTA was 23.4% (33/141) and 18.1% (26/144) respectively, p=0.265.

3.12 Commercial Experience

The LUTONIX DCB has been commercially available since 2012 and is currently approved in many countries including the US, Australia, Brazil, Canada, Japan, Korea, and Taiwan, and in the European Union. Over 400,000 LUTONIX DCBs have been used globally. The product has not been withdrawn from the market for safety reasons in any country.

An evaluation of MDRs showed that adverse events since US approval that could be potentially linked to paclitaxel during a DCB procedure occurred in only 14 patients (overall MDR rate based on units sold: 0.008%). Adverse events included swelling (N=5), hypersensitivity (N=4), gangrene (N=1), liver dysfunction (N=1), pain (N=1), rash (N=1), and ulcer (N=1).

4 Conclusions

Drug-coated balloons were developed to achieve durable patency without the use of a permanent implant (e.g., stent). The LUTONIX DCB was the first DCB approved in the US.

The LUTONIX DCB was designed to perform PTA while delivering paclitaxel to the treated artery with a dose density of 2 µg/mm^2. In the SFA, the LUTONIX DCB was evaluated in a rigorous clinical program including over 3000 DCB patients, which included the multi-center, single-blind, L2RCT. These studies have demonstrated the effectiveness of the device. In the L2RCT trial, a 24% relative improvement in primary patency at 12 months was measured (DCB: 65.2% (172/264), PTA: 52.6% (71/135), p= 0.015).[12] In the Global SFA Real-World Registry with the LUTONIX DCB, the freedom from

[12] Rosenfield, K. et al. NEJM 2015, 373:145

TLR was 89.3% for the overall population, 88.2% for long lesions up to 500mm, and 84.6% for in-stent restenosis at 24 months.[13]

The safety and effectiveness of the LUTONIX DCB were evaluated in 2014 by FDA's Circulatory System Devices Advisory Panel resulting in a unanimous (9-0) recommendation that the benefits of the device outweigh the risks in the indicated population. As the first DCB to undergo an in-depth safety evaluation, at FDA's request, safety data for over 1000 patients were collected for a 5-year follow-up period post-approval. The study was a continued follow-up of participants from the L2 DCB cohort (n=1029) which consists of the L2CA patients (n=657), L2RCT DCB (n=316) and L2RI (n=56), compared against the results from the L2RCT control (PTA) (n=160). The primary safety endpoint, which was a composite of freedom from all-cause perioperative death (≤ 30 days) and index limb amputation (including above or below the knee), index limb reintervention, or index limb-related death through 24 months, showed a benefit for DCB (DCB: 74.7% (674/902), PTA: 67.1% (94/140)). In this study, there were no unanticipated device- or drug-related adverse events. In addition, there was a significant decrease in the serious adverse events (SAE) that were CEC-adjudicated as being related to the device, 11.1% for DCB vs. 20.0% for PTA (p=0.0027).

With respect to mortality, while there was a numerical increase from year 1 to year 5, no statistically significant difference was found when comparing DCB to PTA in the L2 Combined studies. In the worst case, looking at only the L2RCT, using multiple calculation methodologies (raw frequency data analysis, K-M, and HR analysis), there is no significant difference in mortality rate at 5 years. No death was related to paclitaxel, as confirmed by an independent MAB comprised of an interventionalist and an oncologist, who re-adjudicated death events in L1 and L2 Combined studies. Further, the rates of CV and NCV deaths were similar in both groups, and there was no concentration in the cause of death in the DCB group that differed from the PTA group. While this analysis does not invalidate the possibility of an unknown mechanism of paclitaxel-related death, it argues against a common mechanism.

When comparing the randomized DCB cohort (N= 316) of L2RCT to the PTA cohort (N=160), the mortality hazard ratio after 5 years was 1.68 (0.47-1.86). Covariate analysis indicated potential differences in outcome between groups by arrhythmia history at baseline, as well as medications such as statins.

The exposure of patients in the L2RCT to drug-coated technologies at the time of reintervention was evaluated. 19.4% (31/160) of the PTA subjects and 18.4% (58/316) of the DCB subjects were treated with a DCB and/or DES at some point during the 5 year follow-up. These patients showed higher 5-year survival rates than those receiving a single intervention. Subjects in both groups (DCB and PTA) who subsequently underwent a reintervention with a paclitaxel device had higher 5-year survival rates than those that did not have a reintervention. These findings are counter-intuitive if paclitaxel interventions were harmful in the long run. In the three RCTs combined (L1, L2RCT, LJ), reinterventions also appeared to be protective and the frequency of reintervention was greater in the PTA arms. Using an analysis where reintervention was a time-dependent covariate, the HR for L2RCT was reduced to 1.58 (0.91-2.7).

To treat longer lesions, more DCBs need to be used. An analysis was also undertaken to investigate if patients who received a higher dose of paclitaxel were at a higher risk of death than patients who received a low dose, and found no statistically significant relationship between mortality and dose.

In an analysis of the three RCTs using propensity analyses, including the L1, L2RCT, and LJ studies for a combined population of almost 1400 subjects, the DCB hazard ratio was 1.33 (0.8-2.1) at 2 years.

The LUTONIX DCB has also received an indication for the treatment of patients with stenosis of an AV fistula, and is under PMA review for the treatment of BTK patients. No difference in mortality between DCB and PTA treatment was found at 2 years (AVF) or 3 years (BTK) in the randomized trials for these two indications.

In conclusion, while there is a numerical increase in mortality in the L2 Combined studies, the confidence intervals for the HRs overlapped 1.0 in all cases. Furthermore, there is no evidence of a dose-dependent relationship with risk, nor was there any finding of paclitaxel-related death, or a particular cause of death when mortality events were independently

[13] Thieme, M. et al., JACC: Cardiovasc. Interv. 2017

adjudicated. Covariate analysis indicated potential differences in outcome between groups by arrhythmia history at baseline, as well as medications such as statins. Reintervention was found to be protective and occurred more frequently in PTA subjects. While this analysis does not invalidate the possibility of an unknown mechanism of paclitaxel-related death, the low dose of paclitaxel and short persistence, the lack of clustering of any particular cause of death, the survival improvement of patients with multiple reinterventions/exposures to paclitaxel, and the absence of a dose-dependent relationship with mortality argues against a common mechanism.

5 Proposal

If the panel determines additional information is warranted, we support an industry-wide partnership with key stakeholders (physician societies, FDA, etc.) to further interrogate existing, large, observational datasets (e.g., CMS data, RAPID) to confirm lack of a mortality signal over an extended period (through 5 years).

6 APPENDIX - Publications of LUTONIX Device, Animal and Clinical Studies

Following is a listing of the publications of LUTONIX clinical studies, animal study, and device information.

1. Gutierrez-Chico JL, et al, Moxy drug-coated balloon: a novel device for the treatment of coronary and peripheral vascular disease, EuroIntervention 2011 June.
   *Note: LUTONIX catheter was formerly known as the 'Moxy' catheter.
2. Scheinert D, et al., LEVANT I (The LUTONIX Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis) Trial for Femoropopliteal Revascularization. JACC – Press Copy (Nov 9, 2013)
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